Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-120. (canceled)

121. (previously presented) A binding partner for a TSH receptor, which binding partner comprises or is derived from

(a) a human monoclonal antibody reactive with the TSH receptor;

(b) a human recombinant antibody reactive with the TSH receptor; or

(c) a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor

wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies.

122. (currently amended) The binding partner of claim 121, wherein the binding partner is a human monoclonal antibody or a human recombinant antibody or a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor.

123-124. (canceled)

125. (previously presented) The binding partner of claim 121, which has the characteristics of patient serum TSH receptor autoantibodies with respect to inhibition of TSH binding to the TSH receptor.

126. (previously presented) The binding partner of claim 125, wherein the binding partner has an inhibitory activity of at least 15 units of International Standard NIBSC 90/672 per mg.

127. (previously presented) The binding partner of claim 126, wherein the binding partner has an inhibitory activity of at least 120 units of International Standard NIBSC 90/672 per mg.

128. (previously presented) The binding partner of claim 121, which has the characteristics of patient serum TSH receptor autoantibodies with respect to stimulation of cAMP production by cells expressing the TSH receptor.

129. (previously presented) The binding partner of claim 128, wherein the binding partner has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

130. (previously presented) The binding partner of claim 129, wherein the binding partner has a stimulatory activity with respect to cAMP production of at least 240 units of International Standard NIBSC 90/672 per mg.

131. (previously presented) The binding partner of claim 121, which has the characteristics of patient serum TSH receptor autoantibodies with respect to inhibition of TSH binding to the TSH receptor and with respect to stimulation of cAMP production by cells expressing the TSH receptor.

132. (previously presented) The binding partner of claim 131, wherein the binding partner has an inhibitory activity of at least 15 units of International Standard NIBSC 90/672 per mg.

133. (previously presented) The binding partner of claim 132, wherein the binding partner has a stimulatory activity with respect to cAMP production of at least 30 units of International Standard NIBSC 90/672 per mg.

134. (previously presented) The binding partner of claim 121, wherein the binding partner comprises a VH domain as shown in Seq. ID NO: 1, or one or more VH CDRs selected from SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4.

135. (previously presented) The binding partner of claim 134, wherein the binding partner further comprises an antibody VL domain as shown in SEQ ID NO: 6, or one or more VL CDRs selected from SEQ ID NO: 7, SEQ ID NO: 8, and SEQ ID NO: 9.

136. (previously presented) A binding partner according to claim 121, wherein the binding partner is a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor and has an inhibitory activity with respect to TSH binding to the TSH receptor of at least 30 units of International Standard NIBSC 90/672 per mg.

137. (previously presented) A binding partner according to claim 121, wherein the binding partner is a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor and has a stimulatory activity with respect to cAMP production by cells expressing TSH of at least 50 units of International Standard NIBSC 90/672 per mg.

138. (currently amended) A further binding partner for the TSH receptor which is characterised in that the further binding partner

competes for binding to the TSH receptor with a binding partner for the TSH receptor ~~according to claim 121~~ wherein the binding partner comprises or is derived from

(a) a human monoclonal antibody reactive with the TSH receptor;

(b) a human recombinant antibody reactive with the TSH receptor; or

(c) a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor

wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies and in combination withTSH has stimulatory activitity for the TSH receptor,

blocks the stimulatory activity of TSH and the ~~a~~ binding partner for the TSH receptor, ~~according to claim 121,~~ and is thereby capable of rendering the TSH receptor substantially inactive or substantially unresponsive to TSH and TSH receptor autoantibodies.

139. (currently amended) A further binding partner according to claim 138, which when present in an assay to measure the antagonistic properties thereof with respect to blocking the stimulatory activity of the ~~a~~ binding partner for the TSH receptor or TSH ~~according to claim 121~~, results in a greater than 50% reduction in the stimulatory activity thereof.

140. (canceled)

141. (previously presented) A further binding partner according to claim 139 or claim 140, wherein the assay is carried out in Hanks' buffered salt solution, containing about 1 g/L glucose, about 20 mmol/L HEPES, about 222 mmol/L sucrose, about 15 g/L bovine serum albumin and about 0.5 mmol/L 2-isobutyl-1-methyl xanthine, at a pH of about 7.4.

142. (previously presented) A further binding partner according to claim 138, which when present at a concentration in the range of about 0.01 to 10 μg/mL, achieves a percentage inhibition of binding to the TSH receptor of a binding partner for the TSH receptor according to claim 121 in the range of about 3 to about 56%.

143. (previously presented) A further binding partner according to claim 138, which comprises a further antibody or fragment thereof having a binding site for an epitope region of the TSH receptor and which competes for binding to the TSH receptor with a binding partner according to claim 121.

144. (canceled)

145. (previously presented) A further binding partner according to claim 143, which comprises an antibody VH domain as shown in SEQ ID NO. 19, or one or more VH CDRs with an amino acid sequence selected from SEQ ID NO. 20, SEQ ID NO. 21 and SEQ ID NO. 22.

146. (previously presented) A further binding partner according to claim 143, which further comprises an antibody VL domain as shown in SEQ ID NO. 24, or one or more VL CDRs with an amino acid sequence selected from SEQ ID NO. 25, SEQ ID NO. 26 and SEQ ID NO. 27.

147. (withdrawn) A polynucleotide comprising a region encoding an antibody VH domain, VL domain or CDR as shown in any one of SEQ ID NOs: 10-13, 15-18, 29-32 or 34-37, wherein the region

(a) consists of the sequence as set forth in one of the designated Seq ID NOs.;

(b) differs from the sequence of a designated SEQ ID NO. due to degeneracy of the genetic code but encodes the same amino acids; or

(c) differs from the sequence of a designated SEQ ID NO. as a result of an allelic variation.

148. (withdrawn) A biologically functional vector system comprising a polynucleotide according to claim 147 which is capable of introducing the polynucleotide into the genome of a host organism.

149. (withdrawn) A host cell transformed with a polynucleotide according to claim 147.

150. (withdrawn) A polynucleotide comprising a region encoding a fragment of antibody VH domain, VL domain or CDR as shown in any one of SEQ ID NOs: 10-13, 15-18, 29-32 or

34-37, wherein the fragment is a Fab fragment, a Fd fragments, a Fv fragment, a dAB fragment, an isolated CDR region, an F(ab')2 fragment or a scFv fragment, and wherein the region

(a) consists of the sequence as set forth in one of the designated Seq ID NOs.;

(b) differs from the sequence of a designated SEQ ID NO.due to degeneracy of the genetic code but encodes the same amino acids; or

(c) differs from the sequence of a designated SEQ ID NO. as a result of an allelic variation.

151. (withdrawn) A biologically functional vector system comprising a polynucleotide according to claim 150 which is capable of introducing the polynucleotide into the genome of a host organism.

152.(withdrawn) A host cell transformed with a polynucleotide according to claim 150.

153. (withdrawn) A polynucleotide comprising a region encoding an antibody VH domain, VL domain or CDR as shown in any one of SEQ ID NOs: 10-13, 15-18, 29-32 or 34-37, wherein the region consists of the sequence as set forth in one of the designated SEQ ID NOs. modified by a deletion or substitution of a nucleotide base, with the proviso that the amino acid sequence encoded by the polynucleotide retains the ability to interact with the TSH receptor.

154. (withdrawn) A biologically functional vector system comprising a polynucleotide according to claim 153 which is capable of introducing the polynucleotide into the genome of a host organism.

155. (withdrawn) A host cell transformed with a polynucleotide according to claim 153.

156. (withdrawn) A process for making a human monoclonal antibody reactive with TSH receptor comprising the steps of:

(a) isolating lymphocytes from a subject having TSH receptor antibody activity greater than 0.04 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor,

(b) immortalizing the isolated lymphocytes, and

(c) cloning the immortalized lymphocytes to produce an immortalized colony secreting a human monoclonal antibody reactive with the TSH receptor.

157. (withdrawn) The process of claim 156, wherein the subject has TSH receptor antibody activity greater than 0.1 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

158. (withdrawn) The process of claim 157, wherein the subject has TSH receptor antibody activity greater than 0.2 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

159. (withdrawn) The process of claim 158, wherein the subject has TSH receptor antibody activity in the range of 0.3 to 0.5 units of International Standard NIBSC 90/672 per mL of serum with respect to inhibition of TSH binding to the TSH receptor.

160. (withdrawn) The process of claim 156, wherein the lymphocytes are isolated from peripheral blood, thyroid tissue, spleen tissue, lymph nodes or bone marrow.

161. (withdrawn) The process of claim 156, wherein the isolated lymphocytes are immortalized by infection with Epstein Barr virus, and the thus immortalized lymphocytes are fused with a mouse or human cell line to form the immortalized colony.

162. (withdrawn) A process for making a human monoclonal antibody reactive with TSH receptor comprising the steps of:

(a) isolating lymphocytes from a subject having TSH receptor antibody activity greater than 0.1 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor;

(b) immortalizing the isolated lymphocytes, and

(c) cloning the immortalized lymphocytes to produce an immortalized colony secreting a human monoclonal antibody reactive with the TSH receptor.

163. (withdrawn) The process of claim 162, wherein the subject has TSH receptor antibody activity greater than 0.3 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor.

164. (withdrawn) The process of claim 163, wherein the subject has TSH receptor antibody activity greater than 0.5 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor.

165. (withdrawn) The process of claim 164, wherein the subject has TSH receptor antibody activity in the range of 0.5 to 1 units of International Standard NIBSC 90/672 per mL of serum with respect to stimulation of cAMP production by cells expressing the TSH receptor.

166. (withdrawn) The process of claim 162, wherein the lymphocytes are isolated from peripheral blood, thyroid tissue, spleen tissue, lymph nodes or bone marrow.

167. (withdrawn) The process of claim 162, wherein the isolated lymphocytes are immortalized by infection with Epstein Barr virus, and the thus immortalized lymphocytes are fused with a mouse or human cell line to form the immortalized colony.

168. (withdrawn) A method for screening for autoantibodies to TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from an autoimmune disease with an immune reaction to the TSH receptor, said method comprising the steps of:

(a) obtaining a sample of body fluid from said subject;

(b) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner according to claim 121, or a further binding partner according to claim 138, and a second molecule comprising a binding region with which the first molecule interacts, said second molecule being further capable of interacting with autoantibodies to the TSH receptor that may be present in the sample;

(c) contacting the sample with the pair of binding molecules so as to permit the second molecule to interact with the first molecule or with autoantibodies to the TSH receptor that may be present in the sample; and

(d) monitoring the interaction of the second molecule with autoantibodies in the sample, thereby providing an indication of the presence of autoantibodies to the TSH receptor in the sample.

169. (withdrawn) The method of claim 168, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable.

170. (withdrawn) The method of claim 168, wherein the first molecule has an affinity for the TSH receptor of 10^{10} molar^{-1} or greater.

171. (withdrawn) The method according to claim 168, wherein the second molecule comprises full length TSH receptor, or one or more epitopes thereof or a polypeptide comprising one or more epitopes of a TSH receptor.

172. (withdrawn) A method for screening for autoantibodies to TSH receptor in a sample of body fluid obtained from a subject suspected of suffering from, susceptible to, having or recovering from an autoimmune disease with an immune reaction to the TSH receptor, said method comprising the steps of:

(a) obtaining a sample of body fluid from said subject;

(b) providing one or more pairs of binding molecules, wherein a first molecule of said binding pair comprises a human or non-human polyclonal antibody to the TSH receptor and a second molecule of said binding pair comprises a binding region with which said polyclonal antibody interacts, wherein the interaction of said binding molecules is such that an autoantibody titer in said sample essentially corresponding to 0.4U/L of International Standard NIBSC 90/672 is detectable;

(c) contacting said sample with said one or more pairs of binding molecules so as to permit said second molecule of said binding pair to interact with either (i) autoantibodies to the TSH receptor present in said sample, or (ii) said polyclonal antibody; and

(d) monitoring the interaction of said second molecule of said binding pair with said autoantibodies present in said sample, thereby providing an indication of the presence of said autoantibodies to the TSH receptor in said sample.

173. (withdrawn) A method for assaying for TSH or related ligands comprising the steps of

(a) obtaining a sample to be assayed for TSH or related ligands;

(b) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner according to claim 121, or a further binding partner according to claim 138, and a second molecule comprising a binding region with which the first molecule interacts, said second molecule being further capable of interacting with TSH or related ligands that may be present in the sample;

(c) contacting the sample with the pair of binding molecules so as to permit the second molecule to interact with the first molecule or with TSH or related ligands that that may be present in the sample; and

(d) monitoring the interaction of the second molecule with TSH or related ligands in the sample, thereby providing an indication of the presence of TSH or related ligands in the sample.

174. (withdrawn) A method for evaluating a potential binding partner for the TSH receptor comprising the steps of:

(a) providing a pair of binding molecules, said pair comprising a first molecule comprising a binding partner according to claim 121, or a further binding partner according to claim 138, and a second molecule comprising a binding region with which the first molecule interacts;

(b) contacting the potential binding partner to be evaluated with said first molecule and said second molecule so as to permit the second molecule to interact with either the potential binding partner to be evaluated or the first molecule; and

(c) monitoring the interaction of the second molecule with the potential binding partner to be evaluated, wherein competition with the binding of the first molecule to the second molecule indicates that the potential binding partner being evaluated binds to the TSH receptor.

175. (withdrawn) A method for identifying an epitope of the TSH receptor, comprising the steps of:

(a) contacting a binding partner according to claim 121, or a further binding partner according to claim 138, with a full length TSH receptor, or a fragment thereof, and allowing interaction of the binding partner with the full length TSH receptor, or a fragment thereof; and

(b) identifying the amino acids in the full length TSH receptor, or fragment thereof, with which the binding partner interacts.

176. (withdrawn) A method of identifying antibody binding sites, which method comprises screening of phage-displayed random libraries with a binding partner according to claim 121, or a further binding partner according to claim 138.

177. (withdrawn) An anti-idiotypic antibody generated to a binding region of a binding partner for the TSH receptor in accordance with claim 121.

178. (withdrawn) The anti-idiotypic antibody of claim 177, which is 7E51 IgG.

179. (withdrawn) A method for treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to the subject a therapeutically effective amount of a binding partner according to claim 121, or a further binding partner according to claim 138.

180. (withdrawn) The method of claim 179, wherein the binding partner stimulates the TSH receptor.

181. (withdrawn) The method of claim 179, wherein the binding partner or further binding partner interacts with the TSH receptor to inactivate it or render it unresponsive to TSH, TSH receptor autoantibodies or other stimulators.

182. (withdrawn) The method of claim 179, wherein the binding partner or further binding partner inhibits interaction of the TSH receptor with autoantibodies present in the subject's circulation, and wherein interaction of the TSH receptor and autoantibodies is responsible for or associated with said autoimmune disease.

183. (withdrawn) The method of claim 179, wherein the autoimmune disease is disease of the retro-orbital tissues of the eye.

184. (withdrawn) A method of stimulating thyroid or other tissue containing the TSH receptor in a subject in need of such stimulation, comprising administering to the subject a diagnostically or therapeutically effective amount of a binding partner according to claim 121.

185. (withdrawn) The method of claim 184, further comprising the step of administering an additional agent, different from the binding partner, capable of stimulating the TSH receptor.

186. (withdrawn) The method of claim 185, wherein the additional agent is selected from the group consisting of recombinant human TSH and bioactive variants, analogs, derivatives and fragments thereof.

187. (withdrawn) A method of treating autoimmune disease associated with an immune reaction to the TSH receptor in a subject, comprising administering to said subject a therapeutically effective amount of an anti-idiotypic antibody according to claim 177 or 178, whereby administration of said anti-idiotypic antibody substantially inhibits interaction of the TSH receptor with autoantibodies present in the patient's circulation, wherein said interaction of said autoantibodies and said TSH receptor is responsible for, or is associated with, said autoimmune disease.

188. (withdrawn) A method of treating disease of the retro-orbital tissues of the eye associated with autoimmunity to the TSH receptor, which method comprises administration to a patient suffering from or susceptible to such disease a therapeutically effective amount of an anti-idiotypic antibody according to claim 177 or 178.

189. (currently amended) In combination, a binding partner <u>for a TSH receptor, which binding partner comprises or is derived from</u>

<u>(a) a human monoclonal antibody reactive with the TSH receptor;</u>

<u>(b) a human recombinant antibody reactive with the TSH receptor; or</u>

<u>(c) a fragment of a human monoclonal antibody or a human recombinant antibody reactive with the TSH receptor</u>

wherein the binding partner has a characteristic of patient serum TSH receptor autoantibodies and ~~according to claim 121 that~~ stimulates the TSH receptor, and an agent different from the binding partner capable of stimulating TSH receptors for simultaneous or sequential use in stimulating tissue containing the TSH receptor.

190. (previously presented) The combination of claim 189, wherein the agent is selected from the group consisting of recombinant human TSH and bioactive variants, analogs, derivatives and fragments thereof.

191. (previously presented) The combination of claim 189, wherein the agent acts independently of binding to the TSH receptor.

192. (withdrawn) In combination, a binding partner according to claim 121, or a further binding partner according to claim 136 and an agent different from the binding partner or further binding partner, said binding partner and said agent each being capable of inactivating or rendering TSH receptors unresponsive to stimulation by TSH, TSH receptor autoantibodies or other stimulators, for simultaneous or sequential use.

193. (withdrawn) A method of using a binding partner according to claim 121, or a further binding partner according to claim 138, as a replacement source for patient serum or plasma required to contain TSH receptor antibody or antibodies.

194. (withdrawn) A method of using a binding partner according to claim 121, or a further binding partner according to claim 138, in a preparation required to comprise a defined concentration of TSH receptor antibody or antibodies.

195. (withdrawn) A process of preparing a preparation required to comprise a defined concentration of TSH receptor antibody or antibodies, which process comprises providing a binding partner according to claim 121, or a further binding partner according to claim 138, as a suitable preparation having the required defined concentration of TSH receptor antibody or antibodies.

196. (withdrawn) A process for preparing a human recombinant antibody or a fragment thereof comprising cloning a human monoclonal antibody to the TSH receptor or a fragment derived therefrom that binds to TSH receptor, and expressing the cloned antibody or fragment.